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REVIEW ARTICLE

A comparison between hyaluronic acid and other single ingredient eye drops for dry eye, a review

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Abstract

Dry eye disease (DED) is a highly prevalent and debilitating condition. Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan that has a long history as a safe and effective DED treatment. HA is frequently used as a comparator when assessing other topical DED treatments. This study aims to summarise and critically evaluate the literature describing all isolated active ingredients that have been directly compared with HA in the treatment of DED. A literature search was conducted in Embase using Ovid on the 24th of August 2021 and in PubMed including MEDLINE on the 20th of September 2021. Twenty-three studies met the inclusion criteria, 21 of which were randomised controlled trials. Seventeen different ingredients representing six treatment categories were compared with HA treatment. Most measures showed no significant difference between treatments, suggesting either equivalency of treatments or that studies were underpowered. Only two ingredients were represented in more than two studies; carboxymethyl cellulose treatment appears equivalent to HA treatment, while Diquafosol treatment appears superior to HA treatment. Drop-frequency varied from one to eight drops daily. No single study explained the choice of drop frequency. Nine studies used a HA concentration of 0.1% which may be below therapeutic levels. Nine studies reported using preserved formulations, six of them with differences in preservatives between the compared groups. Thirteen studies were financially linked to industry. No major complications were reported. Studies were not designed to find differences in treatment effects for different types or severities of DED. HA is a good comparator treatment when assessing other DED treatments, although

consensus after decades of use is still lacking for best choice of concentration, molecular weight and drop tonicity. Well-designed studies are needed to determine an evidence-based standard for HA treatment to be used as comparator.

KEYWORDS
artificial tears, dry eye disease, hyaluronic acid, tear film

1 | INTRODUCTION

Dry eye disease (DED) is a highly prevalent (Stapleton et al., 2017) and costly (Yu et al., 2011) disorder caused by a loss of homeostasis of the ocular surface and tear film (Craig et al., 2017). The development of dry eye is characterised by tear film instability, tear hyperosmolarity and ocular surface inflammation and damage (Craig et al., 2017). Five to fifty percent of the general population have signs and/or symptoms of DED, depending on the population, location and diagnostic criteria used (Stapleton et al., 2017). Risk factors for DED include female sex, age, screen use and contact lens wear (Stapleton et al., 2017). Given the significant reduction in productivity caused by DED (Uchino et al., 2014) and the cost of treatment (McDonald et al., 2016), the economic burden of DED in the United States alone is estimated to exceed 55 billion US dollars per year (Yu et al., 2011).

Effective and affordable treatment is essential for improving the quality of life and alleviating the financial burden for patients suffering from DED. Topical DED treatment along with lid hygiene, education and environmental modification are considered the first-line treatment of DED (Jones et al., 2017). Topical DED treatment is used by millions of people globally (Jones et al., 2017). The introduction of DED treatment with natural and synthetic polymers and emollients brings benefits to the ocular surface such as improved viscosity, surface adhesion, tear-film distribution, lubrication, increased retention time and decreased evaporation (Pucker et al., 2016) (Figure 1). Ocular lubricants aid in restoring and stabilising the tear film and in protecting the ocular surface (Jones et al., 2017). This helps to delay or prevent damage to the ocular surface (Nebbioso et al., 2016). The wide range of available topical treatments for DED contain various active ingredients that improve physical properties of the tear film to promote tear film stability and other beneficial effects at the ocular surface, including pharmacological effects (Jones et al., 2017). High-viscosity solutions tend to induce blurry vision and are often limited to over-night application (Perry & Donnenfeld, 2003).

One frequently used active ingredient is hyaluronic acid (HA) (Ang et al., 2017), a naturally occurring glycosaminoglycan of varying molecular weight, consisting of repeating units of N-acetyl-D-glucosamine and D-glucuronic acid (Abatangelo et al., 2020). HA is found naturally in human tissues including the vitreous humor, cornea and tear film (Posarelli et al., 2019). There are several beneficial properties of HA in DED treatment, including water retention and lubrication (Lin et al., 2019). HA reduces shear force on the ocular surface (van Setten, 2020), and provides anti-inflammatory (Debbasch et al., 2002; Gomes et al., 2004; Pauloin et al., 2009) and antioxidant effects (Carracedo et al., 2019; Rah, 2011). HA has a long history of safe use in ophthalmology for the treatment of ocular surface diseases, including DED, and is a commonly found ingredient in viscoelastics for intraocular surgery (Higashide & Sugiyama, 2008). Artificial tear drops containing HA are frequently used as control when assessing the safety and efficacy of other dry eye treatment options due to the established effects of HA and its long history of safety and efficacy in ophthalmology (Avila et al., 2019; Caretti et al., 2019; Condon et al., 1999; Doan et al., 2018; Groß et al., 2018; Laihia et al., 2020; McDonald et al., 2002; Moon et al., 2007; Robert et al., 2016).

Actions and effects of topical ocular treatment depends on the active ingredients' physical-, chemical- and pharmacological properties, their concentration, as well as the influence of non-active ingredients that may be present in the formulation, such as preservatives, electrolytes and buffers (Kathuria et al., 2021). The TFOS DEWS II Management and Therapy report organises topical ocular treatment into several categories including viscosity enhancing agents such as polyvinyl alcohol (PVA), osmoprotectants such as trehalose, secretagogues such as diquafosol, lipid supplementation such as phospholipid liposomes, anti-inflammatories such as cyclosporine and serum drops such as platelet-rich-plasma (Jones et al., 2017). Viscosity-enhancing agents relieve dry eye symptoms, increase tear film thickness, protect against desiccation and provide protection of the ocular surface. Some viscosity-enhancing agents, including carboxymethyl cellulose (CMC), Tamarind Seed Polysaccharide (TSP) and HA have been found to have additional mechanisms of action such as epithelial cell adhesion and anti-inflammatory action (Abatangelo et al., 2020; Komakech et al., 2019; Rahman et al., 2021) (Figure 1). Osmoprotectants balance osmotic pressure and protect cells under osmotic stress, while lipid supplementation containing macro-, nano- or cationic emulsions prevent tear evaporation (Jones et al., 2017). Secretagogues pharmacologically stimulate aqueous-, mucin- or lipid secretion, and anti-inflammatories pharmacologically immunosuppress or immunomodulate tissues of the ocular surface or reduce proinflammatory desiccating stress (Jones et al., 2017). Serum drops aim to biochemically approximate and replace human tears and are clinically usually reserved for the treatment of severe DED using autologous serum drops (Jones et al., 2017). Figure 1 visualises the ocular surface location of action and effects of these ingredients.

The rapid increase in commercially available topical DED formulations makes the choice of treatment complex for patients and clinicians alike. A systematic review and meta-analysis on the same topic with search results up to May 2016 concluded with no apparent superiority

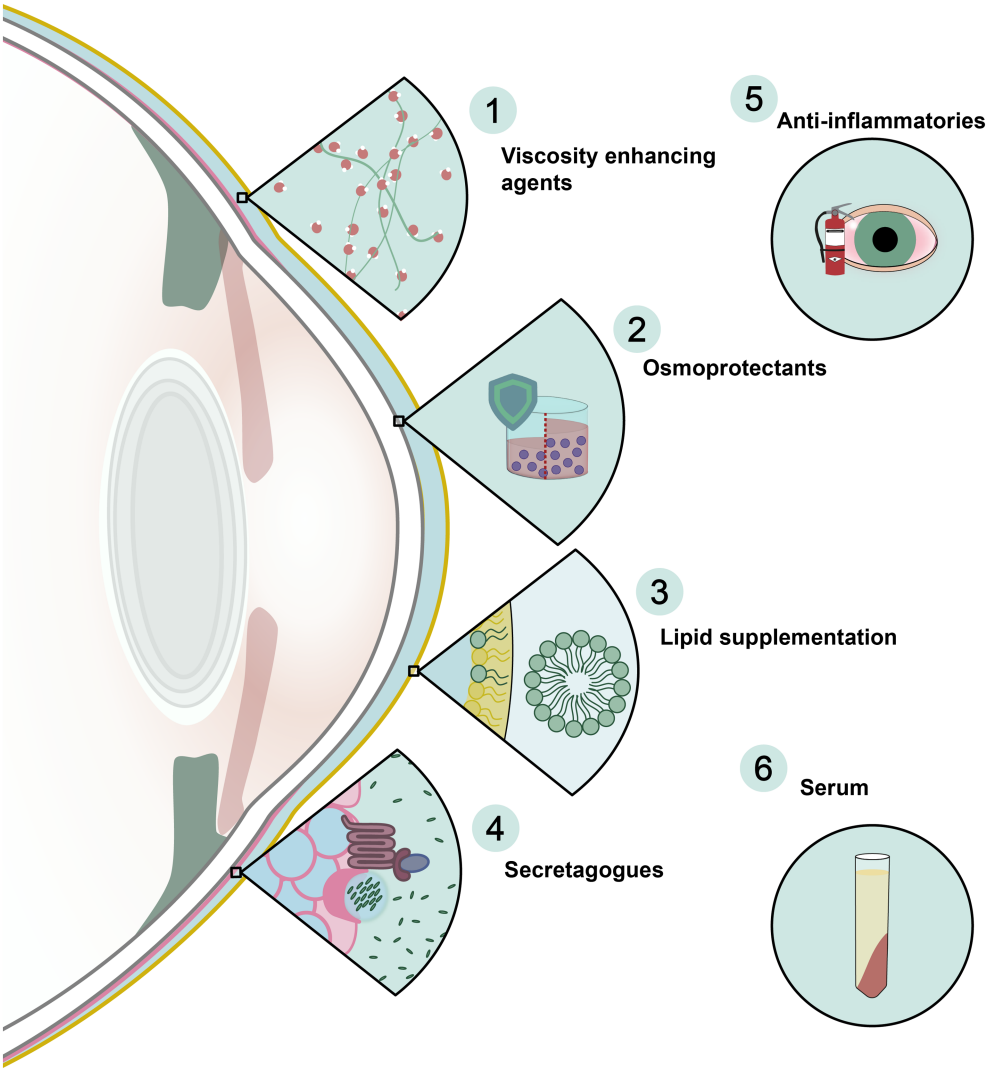

FIGURE 1 Illustration of action of active ingredients included in this review. *Illustration by Emily Moschowits.*

of any one treatment over another (Ang et al., 2017); however, new clinical trials on this topic have been published since then. By critically evaluating the available literature, the aim of the current review is to summarise and compare the safety and efficacy of a broad range of topical dry eye treatment ingredients with hyaluronic acid as comparator.

2 | METHODS

A literature review was conducted in Embase using Ovid on the 24th of August 2021 and in PubMed including MEDLINE on the 20th of September 2021. The search term '(hyaluronic acid OR hyaluronan OR hyaluronate) AND (dry eye OR sicca)' was used in both searches. All original full-text articles in English were considered. Reviews, meta-analyses, case studies and papers on unrelated subjects were not considered. Titles and abstracts were screened to ensure relevance to the topic. Only human clinical trials investigating topical treatments for DED directly compared with HA treatment with reported statistical tests for subjective or objective measurements were included. Studies were narrowed down by checking against the exclusion criteria: (1) more than one active ingredient per treatment solution: 22 exclusions, and (2) no statistical tests reported on subjective or objective outcomes: 3 exclusions. The methodology can be seen graphically in Figure 2.

A table was created to summarise the results of each article, focusing on study design, set-up and efficacy. Important factors examined include type of study, sample size, intervention, subjective and objective patient outcomes, additional key findings, limitations and funding (Table 1).

3 | RESULTS

3.1 | Review of existing literature

The PubMed search which included MEDLINE, produced 351 articles and the Ovid search which included Embase, produced 661 articles. These articles were narrowed down by checking against the inclusion and exclusion criteria as outlined in Figure 2. This resulted in a final list of 23 clinical trials with a total of 30 study arms as presented in Table 1. Among the 23 included studies, there were two non-randomised prospective-longitudinal studies (Benitez-del-Castillo et al., 2002; Duan & Tang, 2021) with the remaining 21 studies being randomised controlled trials (RCTs) (Table 1). Seven studies

Search term: "(hyaluronic acid OR hyaluronan OR hyaluronate) AND (dry eye OR sicca)"	
Results from PubMed: 351	Results from Ovid: 661
Inclusion criteria: English language full text human clinical DED trial comparing topical treatment against HA treatment	
Number of papers meeting inclusion criteria: 48	
Exclusion criteria:	1) >1 active ingredient: 22 exclusions
Number of publications remaining:	26
Exclusion criteria:	2) no statistical tests reported: 3 exclusions
Number of publications remaining:	23

FIGURE 2 Flow chart: execution of literature search.

were open-label (Benitez-del-Castillo et al., 2002; Cui et al., 2018; Duan & Tang, 2021; Hwang et al., 2014; Jun et al., 2019; Park et al., 2017; Rolando & Valente, 2007), nine were single blinded (Brignole et al., 2005; Essa et al., 2018; García-Conca et al., 2019; Gong et al., 2015; Kinoshita et al., 2013; Lee et al., 2011; McCann et al., 2012; Robert et al., 2016; Sanchez et al., 2010), and seven were double-blinded (Johnson et al., 2008; Lambiase et al., 2017; Lee et al., 2006; Matsuo, 2004; Nelson & Farris, 1988; Takamura et al., 2012; Wu et al., 2021). Two studies had cross-over design (Essa et al., 2018; Matsuo, 2004). Four studies were designed as non-inferiority studies or had elements of non-inferiority study design (Gong et al., 2015; Kinoshita et al., 2013; Park et al., 2017; Robert et al., 2016). Sample size varied from 6 to 497 participants (Table 1), with a median of 65 participants across the 23 studies. Trials were one, two or three months in duration (Table 1), except for two studies lasting only 2 weeks (Benitez-del-Castillo et al., 2002; Lambiase et al., 2017).

In Table 1, results of reported tests for statistically significant differences between treatments at last follow-up are presented. Only results with reported tests for statistical significance are included in this review.

Study populations included DED of varying types and severities, post-operative DED patients among them, as specified in the '*Participants*' column of Table 1. Treatments with 17 unique ingredients were compared with HA. Ingredients are organised into six major groups according to the TFOS DEWS II report on management and therapy (Jones et al., 2017); 1. Viscosity-enhancing agents, 2. Osmoprotectants, 3. Lipid supplementation, 4. Secretagogues, 5. Anti-inflammatories, 6. Serum eye drops. For better overview, we further divided the largest represented group, viscosity-enhancing agents, into 'simple' and 'complex' depending on available evidence for additional mechanisms of action such as anti-inflammatory activity. HA in this context is considered a complex viscosity-enhancing agent. Unless otherwise specified, the formulations used were without preservatives, and the drop frequencies in the study arm and the HA arm were the same. Drop frequency ranged from one to eight drops daily across all treatment arms (Table 1). Four studies used different drop frequencies in the study arm and HA arm (Duan & Tang, 2021; Essa et al., 2018; Kinoshita et al., 2013; Park et al., 2017). Figure 3 provides an overview of the major beneficial properties of each active ingredient.

3.2 | Changes in signs and symptoms

3.2.1 | Simple viscosity-enhancing agents

Hydroxypropyl methylcellulose (HPMC) 0.3% and 0.15% HA four times daily were compared in only one study (McCann et al., 2012), with no differences in any subjective or objective measures.

In a single study, 0.3% carbomer was compared with hypotonic 0.18% HA both given two to eight times daily, showing less improvement in ocular surface staining compared with HA and no difference in other measures (Johnson et al., 2008).

Comparison between polyvinyl alcohol (PVA) and HA was represented in two studies (Benitez-del-Castillo et al., 2002; Nelson & Farris, 1988). The first showing inferior corneal epithelial barrier function after 1.4% PVA treatment compared with 0.18% HA four times daily, the other showing no differences between 1.4% PVA and 0.1% HA seven to eight times daily (Nelson & Farris, 1988).

Dextran-70, represented in a single study of postoperative cataract patients, given three times daily, was found to be inferior to HA given one to four times daily in all subjective and objective measures (Duan & Tang, 2021), concentrations were not given.

3.2.2 | Complex viscosity-enhancing agents

Carboxymethylcellulose (CMC) was compared with HA in four separate studies (Brignole et al., 2005; Essa et al., 2018; Lee et al., 2011; Sanchez et al., 2010). Results were mixed, and most measurements were found to have no difference in treatment

TABLE 1 Differences in changes of signs and symptoms of various ingredients vs. HA treatment.

First author (year)	Participants	Design	Study arm	HA arm*	Duration	Symp.	TBUT	OSS	Schi.	Other outcomes	Major limitations	Sponsor/funding
Simple viscosity enhancing agents												
McCann L. C. (2012) (McCann et al., 2012)	73 mild-to-moderate EDE	SB RCT	0.3% HPMC ×4/d	0.15% HA	3 mo	⟷	⟷	⟷		⟷ tear film osmolality	Preservative info N/A	Sponsored by SIFI Spa
Johnson M. E. (2008) (Johnson et al., 2008)	65 moderate DED	DB RCT	0.3% Carbomer ×2-8/d	0.18% HA hypotonic	1 mo	⟷	⟷	↓				Sponsored by TRB Chemedica
Benitez-del-Castillo J. M. (2002) (Benitez-del-Castillo et al., 2002)	6 moderate-to-severe SS	OL PL	1.4% PVA ×4/d	0.18% HA	2 we			↓[f]			PVA with BAK	No
Nelson J. D. (1988) (Nelson & Farris, 1988)	35 moderate KCT	DB RCT	1.4% PVA ×7-8/d	0.1% HA	2 mo	⟷	⟷	⟷	⟷	⟷ tear osmolality	PVA with chlorobutanol	No
Duan Z. (2021) (Duan & Tang, 2021)	99 non-EDE after cataract surgery[c]	OL PL	Dextran-70 ×3/d	HA x1-4/d	2 mo	↓	↓	↓	↓	↓ incidence of ocular irritation	Dextran with BAK. Postop. treatment. Concentrations N/A.	No
Complex viscosity enhancing agents												
Essa L. (2018) (Essa et al., 2018)	50 DED	SB RCT XO	0.25% CMC ×2-3/d	0.4% HA ×2/d	1 mo	⟷	⟷	⟷	⟷[p]	⟷ LIPCOF	CMC with sodium perborate	Treatment products provided by manufacturers.
				0.15% ×3/d		⟷	⟷	⟷	⟷[p]	⟷ LIPCOF		
Lee J. H. (2011) (Lee et al., 2011)	65 mild-to-moderate DED	SB RCT	0.5% CMC ×6/d	0.1% HA	2 mo	⟷	⟷	↑/⟷				Partially sponsored by Alcon
Sanchez M. A. (2010) (Sanchez et al., 2010)	15 mild-to-moderate DED	SB RCT	0.5% CMC ×4/d	0.15% HA	1 mo	⟷	↑	↑				Received equipment from Allergan
Brignole F. (2005) (Brignole et al., 2005)	22 moderate DED	SB RCT	1% CMC ×3/d	0.18% HA hypotonic	2 mo	↓	⟷	↓				One author employed by TRB Chemedica International SA
Rolando M. (2007) (Rolando & Valente, 2007)	30 mild–moderate DED	OL RCT	0.5% TSP ×3-4/d	0.2% HA	3 mo	⟷	⟷	⟷			Preservative info N/A	Supported by Farmigea and Pfizer
			1% TSP ×3-4/d			↑/⟷	⟷	⟷				
Osmoprotectants												
Matsuo T. (2004) (Matsuo, 2004)	36 moderate-to-severe DED	DB RCT XO	100 mM TH ×4/d	0.1% HA	1 mo x2	⟷	↑	↑			HA with BAK	No
Lipid supplementation												
Essa L. (2018) (Essa et al., 2018)	50 DED	SB RCT XO	Phospholipid Liposomes ×2/d	0.4% HA	1 mo	⟷	⟷	⟷	⟷[p]	⟷ LIPCOF		Treatment products provided by manufacturers.
			Phospholipid Liposomes ×3/d	0.15% HA		⟷	⟷	⟷	⟷[p]	⟷ LIPCOF		
Robert P. Y. (2016) (Robert et al., 2016)	85 moderate-to-severe DED	SB RCT	Hypotonic cationic emulsion ×4/d	0.18% HA	3 mo	↑/⟷	⟷	⟷	⟷	⟷ tear film osmolarity, ↑ investigator assessment, ↑/⟷ QoL	Non-inferiority study design.	Sponsored by Santen. Three authors employed by Santen
Secretagogues												
Jun I. (2019) (Jun et al., 2019)	117 DED after cataract surgery[c]	OL RCT	3% DF ×6/d	0.15% HA	3mo	↑	↑	⟷	⟷	⟷ higher order aberrations, ⟷ lipid layer thickness, ↑ MGD parameters	Postop. treatment regimen.	Funded by the National Research Foundation of Korea
			3% DF+CH ×6/d			⟷	⟷	⟷	⟷			
Cui L. (2018) (Cui et al., 2018)	94 DED after cataract surgery[c]	OL RCT	3% DF ×4/d	0.1% HA	3 mo	↑	↑	↑	⟷	⟷ VA, ⟷ higher order aberrations, ↑ CIC grade	Postop. treatment regimen.	Funded by the National Research Foundation of Korea and the Chonnam National University Hospital Biomedical Research Institute

(Continues)

TABLE 1 (Continued)

First author (year)	Participants	Design	Study arm	HA arm*	Duration	Symp.	TBUT	OSS	Schi.	Other outcomes	Major limitations	Sponsor/funding
Gong L. (2015) (Gong et al., 2015)	497 moderate DED	SB RCT	3% DF ×6/d	0.1% HA	1 mo	⟷	⟷	↑			Partial non-inferiority study design	Supported by Santen
Takamura E. (2012) (Takamura et al., 2012)	286 moderate DED	DB RCT	3% DF ×6/d	0.1% HA	1 mo	↑/⟷	⟷	↑/⟷		↑ OSS clearing rate	BAK in both solutions	Funded by Santen
Hwang H. S. (2014) (Hwang et al., 2014)	150 moderate ADDE	OL RCT	3% DF ×4/d	0.1% HA	3 mo	↑	↑	↑	↑	↑ GCD and CIC grade		Funded by the National Research Foundation of Korea, Ministry of Science and Bucheon St Mary's Hospital
Kinoshita S. (2013) (Kinoshita et al., 2013)	188 moderate DED	SB RCT	2% Rebamipide ×4/d	0.1% HA ×6/d	1 mo	↑/⟷	⟷	↑	⟷	↑ patients' impression	Partial non-inferiority study design	Sponsored by Otsuka
Anti-inflammatories												
Park Y. (2017) (Park et al., 2017)	176 moderate-to-severe DED	OL RCT	Cyclosporine 0.05% ×2/d	0.1% HA ×5-6/d	3 mo	⟷	⟷	⟷	⟷	⟷ MGD parameters	Non-inferiority study design	Sponsored by Taejoon Pharm
				0.15% HA ×5-6/d		⟷	⟷	⟷	↓	⟷ MGD parameters		
				0.3% HA ×5-6/d		⟷	⟷	⟷	⟷	⟷ MGD parameters		
Lee H. K. (2006) (Lee et al., 2006)	41 KCL and 23 healthy	DB RCT	0.1% Prednisolone ×3/d	0.1% HA	1 mo	↑	⟷		⟷	↑ CIC, ↑ NGF	BAK in both solutions	Supported by Ministry of Health and Welfare, Korea
Lambiase A. (2017) (Lambiase et al., 2017)	35 moderate DED	DB RCT	150μg/mL lubricin x2-6/d	0.18% HA	2 we	↑	↑	↑	⟷	Less drops per day with lubricin	Financial interests of multiple authors. Lubricin not commercially available	Supported by Dompé farmaceutici s.p.a. and Lμbris BioPharma
Serum eye drops												
Wu Y. (2021) (Wu et al., 2021)	53 moderate DED	DB RCT	DCBE ×4/d	0.3% HA	1 mo	↑/⟷	⟷	⟷	⟷			Funded by the National Natural Science Foundation of China
García-Conca V. (2019) (García-Conca et al., 2019)	84 hyposecretory DED	SB RCT	PRP ×6/d	0.18% HA hypotonic	1 mo	↑	⟷RE ↑LE	↑	↑	↑ VA, ↑ hyperemia, ↑ osmolarity, ↑ CIC measures	Preservative info N/A	Supported by Ministry of Economy of Spain

Abbreviations: (empty cell), not described; ⟷, no statistically significant difference at last follow-up ($p > 0.05$); ↑/⟷, statistically significantly superior in sub-measurements only; ↑, statistically significantly superior to Hyaluronic acid (HA) treatment at last follow-up ($p < 0.05$); ↓/⟷, statistically significantly inferior in sub-measurements only; ↓, statistically significantly inferior to HA at last follow-up ($p < 0.05$); ADDE, aqueous deficient dry eye disease; BAK, benzalkonium chloride (used as preservative) *, unless otherwise specified drop frequency was the same as in study arm; c, all patients also received standard post-surgical treatment regimen; CH, chlorhexidine (used as preservative); CIC, conjunctival impression cytology; CMC, carboxymethyl cellulose; DB, double-blinded; DCBE, deproteinised calf blood extract; DED, dry eye disease; EDE, evaporative dry eye disease; [f], fluorophotometry; GCD, goblet-cell density; HPMC, hydroxypropyl methylcellulose; LE, left eye; MGD, meibomian gland dysfunction; N/A, not given or not available; NGF, nerve growth factor immunostaining; OL, open-label; OSS, ocular surface staining; [p], phenol red test; PEG, polyethylene glycol CS, chondroitin sulfate; PP, patient preference or subjective satisfaction; PRP, platelet-rich plasma; PVA, polyvinyl alcohol; QoL, quality of life assessment; RCT, randomised controlled trial; RE, right eye; SB, single-blinded; Schi., Schirmer's test; SS, Sjögren's syndrome; Symp., subjective symptoms; TBUT, tear film break-up time; TSP, tamarind seed polysaccharide; VA, visual acuity.

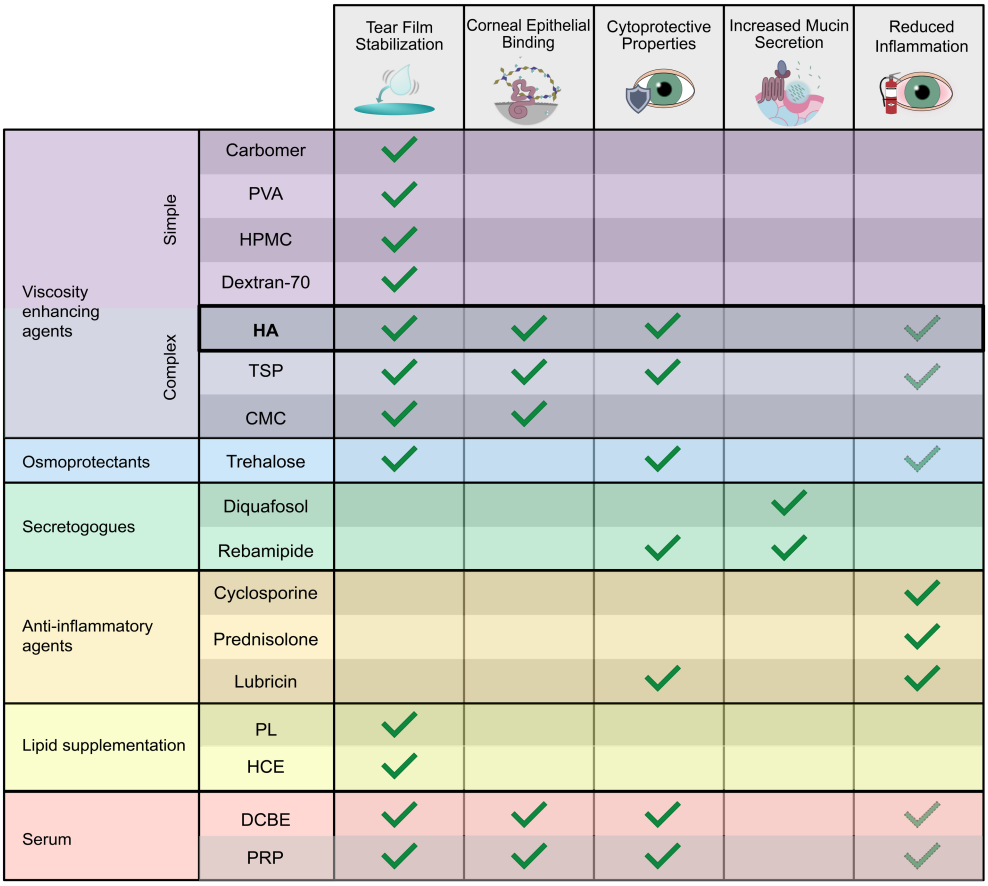

FIGURE 3 The major beneficial properties of the ingredients mentioned in this review. Hyaluronic acid (HA) is outlined. PVA: polyvinyl alcohol. HPMC: hydroxypropyl methylcellulose. TSP: tamarind seed polysaccharide. CMC: carboxymethylcellulose. PL: phospholipid liposomes. HCE: hypotonic cationic emulsion. DCBE: deproteinised calf blood extract. PRP: platelet-rich plasma. *Illustration by Emily Moschowits.*

effect between treatments (Table 1). One study found superiority of 0.5% CMC compared with 0.15% HA in tear film break-up time (TBUT) and ocular surface staining (OSS), both given four times daily (Sanchez et al., 2010). One study found superiority in some OSS measures with 0.5% CMC compared with 0.1% HA six times daily (Lee et al., 2011). A study comparing 0.25% CMC treatment given two to three times daily to 0.4% HA twice daily and 0.15% HA three times daily found no differences between CMC and HA treatments in any measures (Essa et al., 2018). One study found inferior subjective and OSS improvement with 1% CMC compared with hypotonic 0.18% HA, both given three times daily (Brignole et al., 2005).

For tamarind seed polysaccharide (TSP), a concentration of 1% TSP was superior to 0.2% HA in some measurements of symptom improvement, with all other measures showing no difference between both 0.5% and 1% TSP compared with 0.2% HA treatment administered three to four times daily (Robert et al., 2016).

3.2.3 | Osmoprotectants

A single study found four times daily 100 Mm trehalose treatment to be superior to 0.1% HA in improving TBUT and OSS, with no difference in subjective changes (Matsuo, 2004).

3.2.4 | Lipid supplementation

Most measures in the two studies showed no difference between lipid supplementation and HA treatment (Essa et al., 2018; Robert et al., 2016), with the exception of superiority in some measures of subjective and quality of life improvement with a hypotonic cationic emulsion over 0.18% HA, both given four times daily (Robert et al., 2016).

3.2.5 | Secretagogues

Five studies compared 3% diquafosol with 1% or 0.15% HA treatment, administered four or six times daily (Cui et al., 2018; Gong et al., 2015; Hwang et al., 2014; Jun et al., 2019; Takamura et al., 2012). Four out of six study arms showed superior improvement in subjective measures or subjective sub-measures after treatment with diquafosol compared with HA (Cui et al., 2018; Hwang et al., 2014; Jun et al., 2019; Takamura et al., 2012). Two study arms did not find any differences in subjective treatment effects between treatments (Gong et al., 2015; Jun et al., 2019). All five studies comparing diquafosol to HA treatment found superiority of diquafosol over HA in at least one objective measure or objective sub-measure (Cui et al., 2018; Gong et al., 2015; Hwang et al., 2014; Jun et al., 2019; Takamura et al., 2012). Three out of six study arms found superiority of diquafosol over HA in

TBUT improvement (Cui et al., 2018; Hwang et al., 2014; Jun et al., 2019). Four out of six study arms found superiority or sub-measure superiority of diquafosol over HA in OSS changes (Cui et al., 2018; Gong et al., 2015; Hwang et al., 2014; Takamura et al., 2012). One out of four study arms found superiority of diquafosol over HA in Schirmer's test improvement (Hwang et al., 2014). One study found across-the-board superiority of diquafosol treatment over HA treatment (Hwang et al., 2014). No study found inferiority of diquafosol compared with HA in any measures.

One study compared treatment with 2% rebamipide four times daily and 0.1% HA six times daily (Kinoshita et al., 2013) and found superiority of some subjective measures and superior OSS improvement with rebamipide over HA.

3.2.6 | Anti-inflammatories

Cyclosporine 0.05% twice a day had similar effect as 0.1%, 0.15% and 0.3% HA five to six times per day, except for inferior improvement for cyclosporine in Schirmer's test compared with 0.15% HA (Park et al., 2017).

In a single study, treatment with 0.1% prednisolone three times daily was superior to 0.1% HA three times daily in subjective improvement, conjunctival impression cytology improvement and nerve growth factor immunostaining improvement (Lee et al., 2006).

A single study found two to six times daily administration of 150ųg/mL lubricin to have superior improvement compared with 0.18% HA in all measures apart from Schirmer's test (Lambiase et al., 2017).

3.2.7 | Serum eyedrops

Deproteinised calf blood extract treatment had superior improvement compared with 0.3% HA in some subjective measures, with no significant treatment differences in any other measures (Wu et al., 2021), both given four times daily.

Protein-rich plasma (PRP) treatment showed superior improvement compared with 0.18% hypotonic HA in all measures apart from TBUT in right eyes (García-Conca et al., 2019), both given six times daily.

3.3 | Preservatives

Preservatives used across studies were benzalkonium chloride (BAK), chlorobutanol, sodium perborate and chlorhexidine (Table 1). Five studies compared treatments in which the study arm solution contained preservatives and the HA solution did not (Benitez-del-Castillo et al., 2002; Duan & Tang, 2021; Essa et al., 2018; Jun et al., 2019; Nelson & Farris, 1988). Two studies used formulations containing BAK in both treatment arms (Lee et al., 2006; Takamura et al., 2012). The only study comparing trehalose with HA treatment used preservative-free trehalose while using HA preserved with BAK (Matsuo, 2004). Two studies did not provide any information about preservatives in the formulations used (García-Conca et al., 2019; Rolando & Valente, 2007). One study used both chlorhexidine-preserved and preservative-free diquafosol in separate study arms (Jun et al., 2019). In that study, only the preservative-free diquafosol showed superior symptomatic and TBUT improvement over HA, while chlorhexidine-preserved diquafosol did not. The remaining studies used preservative-free formulations in all treatment arms.

3.4 | Safety and complications

All treatments were considered safe and well tolerated in all reviewed literature. There were no serious or permanent adverse events associated with the use of any of the treatment ingredients. One study described significantly less adverse events with HA drops than with diquafosol (Gong et al., 2015). Some patients receiving drops containing prednisolone experienced an increase in intraocular pressure, a known adverse effect with topical steroid treatment (Lee et al., 2006).

4 | DISCUSSION

4.1 | Summary

In the reviewed literature various isolated active ingredients were compared woth HA treatment for DED. CMC treatment seems mostly equivalent to HA while the secretagogue diquafosol appears to outperform HA treatment. The remaining ingredients were represented in only one or two studies each. A majority of the compared measures showed no significant difference between the treatments assessed, indicating either equivilancy between treatment effects in those measures, or that the studies were underpowered. Differences in preservatives between treatment arms may have affected some results, though most studies used preservative-free formulations.

4.2 | HA as comparator

No clear clinical best practice has been established for the choice of HA concentration, drop frequency, drop tonicity or molecular weight of HA, which varies widely between trials (Hynnekleiv et al.). There are indications that a concentration of 0.1% HA or less is below therapeutic levels, and that concentrations above 0.1% bring improved treatment effects (Ang et al., 2017; Hynnekleiv et al., 2022). Nine of the included studies used HA with a concentration of 0.1% (Cui et al., 2018; Gong et al., 2015; Hwang et al., 2014; Kinoshita et al., 2013; Lee et al., 2006, 2011; Matsuo, 2004; Nelson & Farris, 1988; Takamura et al., 2012). A treatment compared with an inappropriately low dose of comparator intervention can result in comparator bias (Mann & Djulbegovic, 2013). Studies using HA as comparator to assess other treatments for DED should preferably use HA concentrations higher than 0.1%.

Carboxymethyl cellulose is a complex viscosity-enhancing agent with hydrophilic and bioadhesive

properties (Javanbakht & Shaabani, 2019). CMC and HA treatment for DED seem equivalent in the reviewed literature. A systematic review and meta-analysis from 2017 found no statistically significant differences between these two treatments across studies (Song et al., 2017), although the authors *did* conclude that the efficacy of CMC appeared better than that of HA. While the current review is limited only to studies that investigate effects of isolated active ingredients, the 2017 review included studies with CMC solutions that contained additional active ingredients such as glycerin.

The secretagogue diquafosol is a pharmacologically active P2Y2 purinogenic receptor agonist (Keating, 2015). Diquafosol appears superior to HA treatment in the five studies that investigated this comparison, though four of those studies used a low HA concentration of 0.1%. To our knowledge, this is the first review to report on this comparison. Considering the vastly different mechanisms of action between diquafosol and HA, these treatments are likely to synergise if used together.

Cyclosporine, an immunosuppressive and immunomodulating calcineurin inhibitor that reduces T-cell proliferation, was the first prescription drug approved by the US Food and Drug Administration for DED treatment (Schultz, 2014). One included study found various HA concentrations to be non-inferior to cyclosporine treatment (Park et al., 2017). Clinically, however, cyclosporine is frequently administered together with artificial tears as part of accepted practice and treatment algorithms (Jones et al., 2017), as these two ingredient's mechanisms of action are vastly different and complement each other.

Topical treatments for dry eye with different mechanisms of action are frequently used clinically in parallel to attack the vicious cycle of dry eye at several points simultaneously and to improve the multiple layers of the tear film (Kojima et al., 2020). Study comparisons of principally different treatments such as anti-inflammatories, osmoprotectants, lipid supplementation or viscosity-enhancing agents may therefore appear inappropriate, albeit sometimes required, for example, in the context of governmental approval (Novack et al., 2017).

4.3 | Tailored DED treatment

Reasoning behind the choice of a particular drop frequency was not described in any of the studies, apart from treatments with pharmacological agents (anti-inflammatories and secretagogues), in which standardised treatment regimens were used. Drop frequency should be tailored to the individual DED patient (Kim et al., 2021). Considering the huge variability in ingredients, concentrations, viscosity and other characteristics among the various products available (Kapadia et al., 2022), drop frequency should also depend on the specific product used. The heterogeneity in drop frequency across studies can be attributed to the lack of studies specifically investigating this aspect of DED treatment, as exemplified by a literature review of HA treatment for DED by our group that describes this literature gap (Hynnekleiv et al.), as well as the current review in which no such studies were found. Future clinical trials should aim to determine optimal drop frequency of topical treatment for DED.

In the reviewed literature, a wide range of DED severity and type were represented. The severity of DED ranged from mild to severe across studies (Table 1). Six studies did not discriminate DED severity (Cui et al., 2018; Duan & Tang, 2021; Essa et al., 2018; García-Conca et al., 2019; Jun et al., 2019; Lee et al., 2006). Fourteen studies indiscriminately recruited DED patients regardless of type (Brignole et al., 2005; Essa et al., 2018; Gong et al., 2015; Johnson et al., 2008; Kinoshita et al., 2013; Lambiase et al., 2017; Lee et al., 2011; Matsuo, 2004; Park et al., 2017; Robert et al., 2016; Rolando & Valente, 2007; Sanchez et al., 2010; Takamura et al., 2012; Wu et al., 2021), while six studies recruited patients with DED of defined types (Benitez-del-Castillo et al., 2002; García-Conca et al., 2019; Hwang et al., 2014; Lee et al., 2006; McCann et al., 2012; Nelson & Farris, 1988), including evaporative DED (EDE) (McCann et al., 2012), aqueous deficient DED (ADDE) (Hwang et al., 2014) and Sjögren's syndrome (SS) (Benitez-del-Castillo et al., 2002). DED in Sjögren's syndrome patients is notoriously difficult to treat (Jones et al., 2017). Artificial tears are seldom sufficient, as these patients often need serum eye drops, steroid treatment, punctal plugs and a range of other available treatments (Mavragani et al., 2006).

There is very little available evidence to support recommendations for changing HA treatment regimens depending on DED severity or type (Hynnekleiv et al.). Selection of topical treatment for DED may depend on the underlying aetiology of dry eye (Kathuria et al., 2021). In one study carbomer and lipid combination drops were better than HA at improving optical quality and optical aberrations in patients with severe meibomian gland dysfunction (MGD) (Mihály et al., 2018). It is the insufficiency of the natural lipid layer of the tear film that is the main cause of DED in MGD patients (Bron et al., 2017), which lends an explanation to this finding. The two studies in the current review investigating lipid supplementation compared with HA treatment did not find superiority of either treatment (Essa et al., 2018; Robert et al., 2016), which may be due to the etiologically undiscriminated group of DED patients, study design or the relatively small number of participants.

4.4 | Limitations

Commonly used preservatives in eye-drop formulations, especially benzalconium chloride, have well-known toxic effects at the ocular surface (Burstein, 1980; Fineide et al., 2022; Wilson et al., 1975; Wu et al., 2011). The findings in studies with discrepancies in preservatives between comparative study arms are likely to have been influenced by these differences (Benitez-del-Castillo et al., 2002; Duan & Tang, 2021; Essa et al., 2018; Jun et al., 2019; Matsuo, 2004; Nelson & Farris, 1988). Long-term treatment with certain preservatives negatively affect the ocular surface micro-environment (Jee et al., 2015), which is why preservative-free artificial

tears are generally reccomended for the longevity of ocular health (Baudouin et al., 2004).

Five studies used hypotonic solutions (Brignole et al., 2005; García-Conca et al., 2019; Johnson et al., 2008; Nelson & Farris, 1988; Robert et al., 2016). Hypotonic formulations lower the osmolarity of the tear film, aiming to reduce hyperosmolarity which perpetuates the vicous cicle of DED and causes inflammation, ocular surface damage and tear film instability (Bron et al., 2017). Few clinical studies investigate the differences in treatment effects between hypotonic and isotonic formulations for dry eye treatment, though results of at least four clinical trials show superiority of hypotonic over isotonic drops (Aragona et al., 2002; Gilbard & Kenyon, 1985; Li et al., 2017; Papa et al., 2001; Troiano & Monaco, 2008). Comparing ingredients with formulations of different tonicity may affect results, due to the possibility of hypotonicity providing additional treatment benefits.

Sample size varied greatly across studies, from 6 to nearly 500 participants (Table 1). Only five of the included studies described performing power calculations before recruitment in their methodologies (García-Conca et al., 2019; Gong et al., 2015; Jun et al., 2019; Robert et al., 2016; Wu et al., 2021). Smaller studies, especially studies with 20 participants or fewer, are likely to be underpowered for the magnitude of the expected effect size (Hackshaw, 2008). Too small sample sizes can easily lead to type I errors, while too large sample sizes expose more participants than necessary to possible disadvantages of study participation and could be considered imbalanced resource management (Naduvilath et al., 2000). Therefore, care should be taken to conducting appropriate power calculations a priori whenever possible for clinical trials within ophthalmology (Naduvilath et al., 2000).

Few of the studies reviewed followed TFOS DEWS recommendations for the planning and execution of clinical trials for DED treatment (Novack et al., 2017). Equal comparisons between treatments were often prohibited either by differences in preservative status, formulation tonicity or drop frequency. Included studies lasted 3 months or less (Table 1), which might be at the low end of reasonable duration to assess differences in dry eye treatment, although a definite consensus on this topic seems not to be reached (Novack et al., 2017). No clear relationship was observed between study length and results in the included studies. Most studies lacked double blinding. Studies were not designed to provide evidence of treatment choice for a particular DED severity or type. Four studies were designed as non-inferiority studies or had elements of non-inferiority study design (Gong et al., 2015; Kinoshita et al., 2013; Park et al., 2017; Robert et al., 2016), aimed at proving the similarities of the eye drops tested rather than finding their differences (Head et al., 2012). Thirteen of the 23 studies in the reviewed literature were financially linked to the DED treatment industry (Brignole et al., 2005; Gong et al., 2015; Johnson et al., 2008; Kinoshita et al., 2013; Lambiase et al., 2017; Lee et al., 2011; McCann et al., 2012; Park et al., 2017; Robert et al., 2016; Rolando & Valente, 2007; Sanchez et al., 2010; Takamura et al., 2012), eight of them to the producer of the non-HA formulation (Gong et al., 2015; Kinoshita et al., 2013; Lambiase et al., 2017; McCann et al., 2012; Robert et al., 2016; Rolando & Valente, 2007; Sanchez et al., 2010; Takamura et al., 2012) and five of them to the producer of the HA formulation (Brignole et al., 2005; Johnson et al., 2008; Lee et al., 2011; Park et al., 2017). As only eight of the included studies were double-blinded, and most were industry sponsored, expectations and bias could play an important role in the outcomes of most of the included studies, as it has been shown that studies with financial conflicts of interest are more likely to arrive at positive conclusions (Okike et al., 2008).

The lack of independently funded double-blinded RCTs presents a major gap in the literature. Designing a study with a suitable comparator treatment, with isolated active ingredients in preservative-free formulations, and with study design allowing for objective assessment is demonstrably difficult, especially with the lack of a consensus for the correct HA concentration, molecular weight or drop frequency when treating DED (Hynnekleiv et al.).

5 | CONCLUSION

Hyaluronic acid has long been used as a comparator for assessing efficacy of other topical DED treatments. This literature review that critically evaluates clinical studies comparing isolated topical DED treatments with HA treatment reveals that the treatment effect of CMC for DED seems to be equivalent to HA, and diquafosol appears superior to HA treatment. Several critical limitations in most of the included literature prohibit strong conclusions in terms of superiority of single ingredients, including the low number of studies investigating the effect of isolated ingredients, the wide variety of drop formulations and treatment regimens, the use of preservatives, the use of low HA concentration and the lack of studies investigating potential treatment differences among various DED types and severities. This sheds light on an important gap in the literature for researchers and treatment providers of DED, and warrants more high-quality research in this area. Independent double-blinded RCTs with preservative-free formulations that isolate the effects of treatment and that use HA concentrations higher than 0.1% are needed to determine if other ingredients are superior or inferior to HA in DED treatment and to better answer whether treatment choice may depend on severity or type of DED.

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